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Reaction Discovery Using Neopentylene-Tethered Coupling Partners: Cycloisomerization/Oxidation of Electron-Deficient Dienynes

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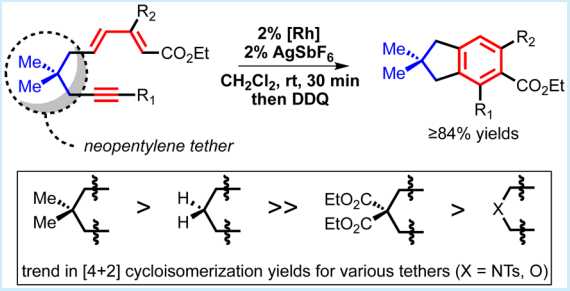
Supporting Information

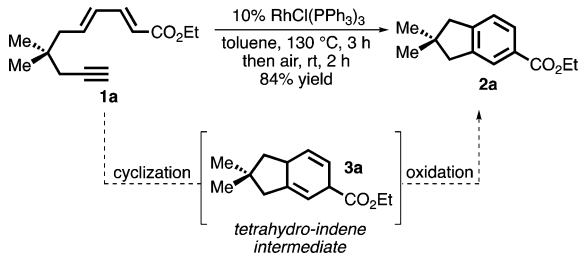
ABSTRACT: A rhodium-catalyzed cycloisomerization and oxidation of tethered dienynes for the synthesis of indanes is described. An auxiliary fragmentation/olefination method (also described herein) provides novel access to tethered alkyne-dienoate substrates. The reported method circumvents current limitations in and expands the scope of inverse-demand Diels–Alder-type cycloadditions. Traditional discovery substrates involving malonate-, ether-, and sulfonamide-based tethers are problematic in the current methodology, underscoring the unique virtue of neopentylene-tethered substrates for reaction discovery.



Considering the rich history of the concerted Diels–Alder cycloaddition,[1] and modern advances in transition-metal catalysis of alternative reaction pathways,[2−7] strategic gaps in [4 + 2] annulation technology can be viewed as fundamentally problematic. Electron-deficient dienes, for example (unless stabilized by aromaticity[8]), are limited by an underappreciated tendency to react with electron-deficient dienophiles,[9] which often results in dimerization and/or oligomerization. Likewise, alkyne dienophiles can be reticent cycloaddition partners, perhaps because alkyne π-bonds are relatively shorter and stronger than their alkene counterparts.[10] Thus, "inverse-demand"[11] [4 + 2] cycloadditions of unactivated alkyne dienophiles with electron-deficient dienoates present a fundamental reactivity challenge,[12−14] placing a strategic limitation on [4 + 2] annulation technology. Here we report a breakthrough methodology for intramolecular Diels–Alder (IMDA)-type reactions of electron-deficient dienynes, using neopentylene-tethered substrates and rhodium (Rh) catalysts. We coupled Rh-catalyzed cycloisomerizations with in situ oxidation to generate substituted indanes (Scheme 1). Notably, traditional tethers featuring malonate, ether, and sulfonamide functional groups compromise this process (vide infra).

Reaction discovery methodologies aimed at expanding the scope and impact of [4 + 2] cycloadditions (Figure 1) often begin with a focus on intramolecular processes of tethered reaction partners, which provide favorable entropy as well as synthetic utility for preparing polycyclic structures. Substrate tethers are often chosen based on synthetic convenience. With few exceptions,[12] traditional tethers for intramolecular [4 + 2] cycloaddition methodologies include *malonate*, *ether*, and *sulfonamide* functional groups, which facilitate tethering via S_N2-type alkylation chemistry but compromise the ideal of using a chemically inert tether.

Scheme 1. Preliminary [4 + 2] Annulation of Neopentyl-Tethered Dienyne 1



We prepared neopentylene- and propylene-tethered dienoate substrates (Scheme 2) by extension of our previously reported tandem fragmentation/olefination methodology.[15] Mixtures of alcohols **4** and phosphonates **5** were treated with LDA at low temperature. Lithiated **4** undergoes fragmentation upon warming, and the resulting aldehyde reacts with the awaiting lithio-phosphonate anion of **5**. Our initial substrate scope included variable methyl substitution on the alkyne, on the tether, and/or on the dienoate to provide focused coverage of representative dienoates. Other dienoates, including ones bearing ether, malonate, and sulfonamide tethers,[16] were prepared by traditional methods.[17]

Our initial success with the oxidative cycloisomerization came using Wilkinson's catalyst (10 mol %) in toluene in a sealed vial at 130 °C (cf. Scheme 1, above). These conditions give rise to inseparable mixtures of (dihydro)indanes **2** and **3**, so air was bubbled through the reaction mixture after heating to complete oxidation to **2**. We later switched from air to DDQ for more reliable oxidation. Preliminary screening of other

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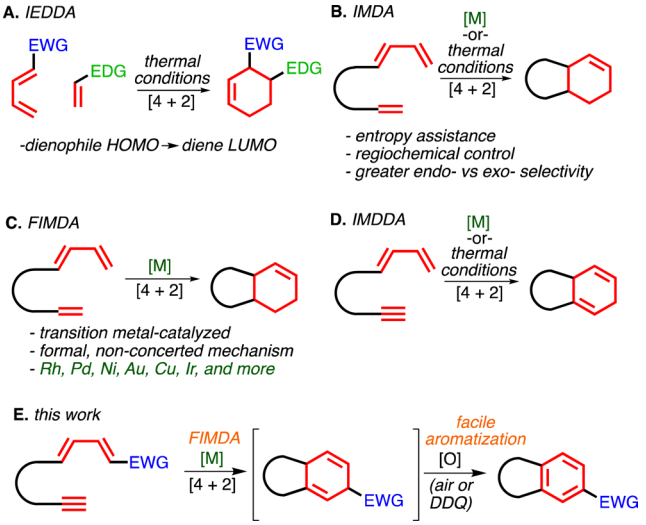
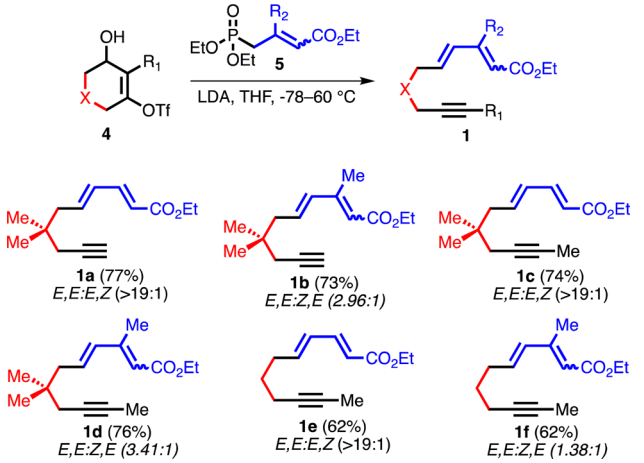


Figure 1. Variants of the Diels–Alder reaction, including inverse electron demand (A) (IEDDA), (B) intramolecular (IMDA), (C) metal-catalyzed formal (FDA), and (D) the dehydro Diels–Alder reaction (DDA). (E) Cycloisomerization and oxidation reported in this manuscript.

Scheme 2. Synthesis of Alkyl-Tethered Dienynes by Tandem Fragmentation–Olefination[a]



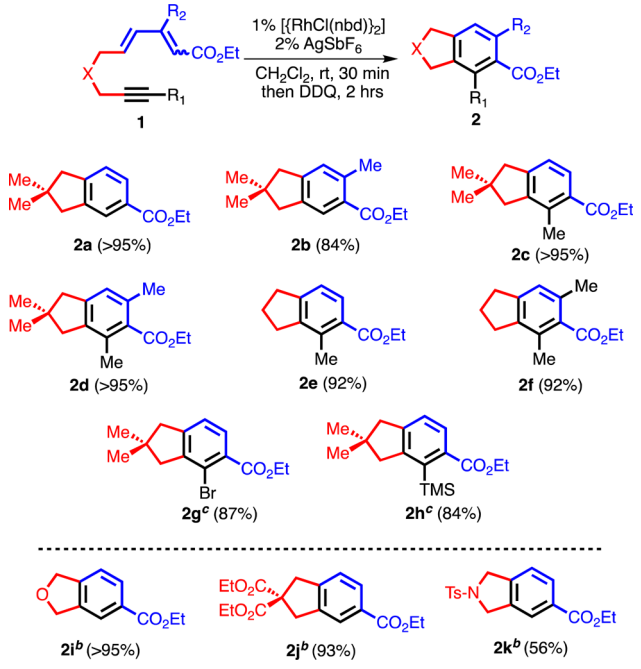
[a]All yield are isolated yields.

metal (Au, Pd, Co, and Ni) catalysts failed to reveal a cheaper and more efficient alternative to rhodium, and qualitative screening of ligands helped us identify diene ligands, particularly norbornadiene, as superior to the triphenylphosphine ligands of Wilkinson's catalyst.

A cationic rhodium(I) norbornadiene catalyst—generated in situ by combining [{RhCl(nbd)}$_2$] with silver hexafluoroantimonate ($AgSbF_6$) in dichloromethane—enabled us to lower the temperature (from 130 °C to rt), time (from 3 h to 30 min), and catalyst loading (from 10% to 2% [Rh]) while increasing the isolated yields of the desired indanes (cf. Scheme 3).

With the better optimized set of conditions, our next focus was to elaborate on the scope of the cycloaddition and oxidation sequence to access the Indane core (Scheme 3). Oxidative cycloisomerization of the newly acquired hydrocarbon-tethered alkyne dienoates (**1a–f**, cf. Scheme 2) provides indanes **2a–f** in good to excellent yields (Scheme 3). Bromo- and silyl-alkynes **1g** and **1h** (derived from dienyne **1a**[17]) were also good cyclization substrates, providing indanes **2g** and **2h** in of 87% and 84% isolated yield, respectively. The highest yields were obtained from the neopentylene-tethered substrates (cf. **2c** vs **2e** and **2d** vs **2f**), which we attribute to favorable Thorpe–Ingold conformational biases[18] imposed by the *gem*-dimethyl substitutent pattern in the tether. In contrast, substrates with traditional ether, malonate, and sulfonamide tethers did not undergo cycloisomerization with similar efficiency (without significantly increasing the amount of catalyst; see Table 1, below).

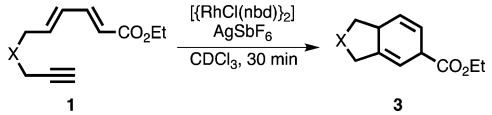
Scheme 3. Rhodium-Catalyzed Cycloisomerization and Oxidation of Tethered Alkyne Dienoates for the Synthesis of Indanes[a]



[a]All yields are isolated yields from ~0.4–0.5 mmol of starting material. [b]Higher catalyst loading: reactions performed using 10% [{RhCl(nbd)}$_2$] and 20% $AgSbF_6$ because little-to-no cyclization was observed under the above conditions; see Table 1 for additional discussion. [c]Isolated product contains a trace impurity, observable in the ^{1}H and ^{13}C NMR spectra.

We next examined the disparity between neopentylene-tethered systems and those bearing heteroatoms in the tether

Table 1. Traditional Tether Cycloaddition Reaction Progressions by ^{1}H NMR[16]



entry	X	[{RhCl(nbd)}$_2$] (mol %) :$AgSbF_6$ (mol %)	% conversion, estimated by ^{1}H NMR
1	N-Ts	1:2	13 (**1k** → **2k**)
2	N-Ts	10:20	60 (**1k** → **2k**)
3	$C(CO_2Et)_2$	1:2	28 (**1j** → **2j**)
4	$C(CO_2Et)_2$	10:20	>95 (**1j** → **2j**)
5	O	1:2	— (**1i** → **2i**)
6	O	10:20	>95 (**1i** → **2i**)

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(Table 1). Catalyst inhibition does not seem to be the problem; addition of excess diethyl malonate to a representative reaction mixture (**1c** → **2c**, not shown) did not noticeably impact the reaction process. Alternatively, heteroatoms in the tether may deactivate the substrate through subtle inductive effects,[19] while also providing alternative substitution and/or elimination pathways that may become competitive at higher temperatures. We also consider the possibility of alternative binding motifs in substrates bearing additional Lewis basic sites to be a potential factor in the slower reaction rates. The relatively poor reactivity of traditional substrates may be overcome at higher catalyst concentration (Table 1). We examined reactions of substrates bearing sulfonamide, malonate, and ether functional groups in the tether at low and high catalyst loadings (2 mol % and 20 mol % [Rh], respectively). Little to no conversion was observed with 2 mol % [Rh]—conditions for which neopentylene-tethered substrates underwent full conversion. Increasing the catalyst loading to 20 mol % [Rh] led to 60% conversion for the sulfonamide and full conversion for malonate and ether substrates. Reactions listed in Table 1 are not optimized, and focused optimization on substrates bearing traditional tethers may lead to improved procedures for these particular classes of substrates.[20] These studies underscore the virtues of neopentylene-tethered substrates for initial reaction discovery.

We envision a mechanism analogous to what has been described previously for Rh-catalyzed cycloisomerization of tethered dienynes (Figure 2).[2a] Initial coordination of Rh(I) to

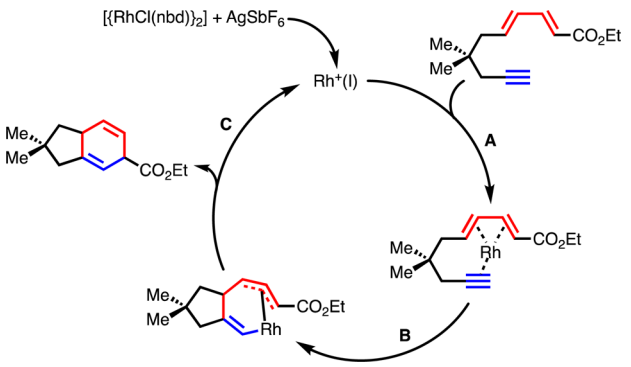

Figure 2. Postulated catalytic cycle. (A) Coordination of π-system with cationic Rh(I), (B) oxidative addition to form 7-membered Rh(III)-metallacycle, (C) reductive elimination.

the dieneyne system is followed by oxidative cyclization to a vinyl(π-allyl)Rh(III) intermediate, which can undergo reductive elimination to regenerate Rh(I) and release the dihydroindane product, which is later oxidized. One can imagine that the initial dienyne-[Rh] coordination is disfavored for electron-poor π-systems, which can help explain why a cationic Rh(I) with weakly bound ligands (e.g., $[RhCl(nbd)]_2/AgSbF_6$) is better than Wilkinson's catalyst $[RhCl(Ph_3P)_3]$, the catalyst with which we made the original discovery. Electronegative atoms inductively decrease electron-density in the π-system—perhaps more so than may be expected[19]—consistent with the poor reactivity of traditional dienyne substrates bearing electronegative atoms in the tether.

Finally, we note that the *gem*-dimethylindane core is found in the illudalane family of sesquiterpenes (Figure 3), which are of interest both as classic targets for total synthesis[21] and for a range of promising biological activities. Indane **2d** (Scheme 3)

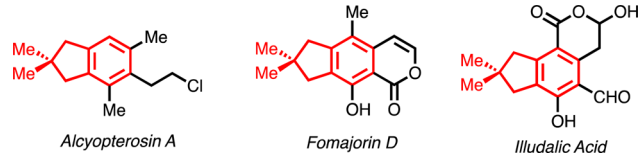

Figure 3. Illudalane sesquiterpene natural products containing a core *gem*-dimethylindane.

was previously prepared in 9 steps from isophorone as a key intermediate in the first synthesis of alcyopterosin A.[22]

Tethered alkyne dienoates undergo cycloisomerization/oxidation to substituted indanes in the presence of Rh(I) catalysts. The present methodology reveals the unique virtues of the neopentylene tether for reaction discovery, as it enabled us to close a persistent and important gap in Diels–Alder-type cycloaddition technology. Extension of previous tandem fragmentation/olefination methodology provides access to neopentylene-tethered dienyne substrates. This is the second reaction process we have identified[23] for which the neopentylene tether was strategically important to reaction discovery, and it is the first that involves transition metal catalysis and mild reaction conditions. We expect neopentylene-tethered substrates to enable a new wave of reaction discovery and provide access to underexplored structure space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02261.

Experimental procedures, spectroscopic characterization data, copies of ^{1}H and ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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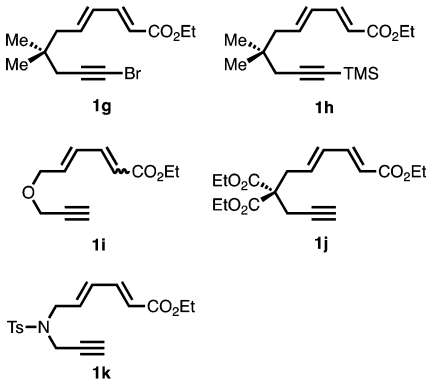
(16) Graphical depictions of substrates **1g**−**k**:



(17) For the synthesis of **1g**−**k**, see Supporting Information.

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(20) We thank a reviewer for encouraging us to include this point of logical emphasis regarding the possibility of divergent optimization outcomes from the initial hit—that it may be possible to advance from our initial observation to an alternative protocol that is better suited for substrates bearing traditional tethers. For example, functional groups embedded in the tethers of traditional substrates may facilitate competing mechanistic pathways (such as allene formation by heterolytic cleavage of the tether linkage), which would be unlikely in the hydrocarbon tethers. As the reviewer astutely noted, "traditional tethered substrates [examined herein] all have this separate flaw," which merits broader consideration and further examination.

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